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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/467,901	12/21/1999	JOOST VAN NEERVEN	02405.0190	2936

7590 09/08/2004

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EXAMINER	
DO, PENSEE T	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/467,901	NEERVEN, JOOST VAN	
	Examiner	Art Unit	
	Pensee T. Do	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 16, 2004 has been entered.

Claim Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8-14, 16, 21, 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) further in view of Johnson et al. (US 6,034,066) and Frank et al. (US 6,060,326).

Johansen et al. teach a method of detecting an antibody in a sample using a labeling compound and comprising the steps of mixing the ligand antigen, antibody or hapten bound to biotin with the sample; an antibody is directed against the antibody to be detected bound to a paramagnetic particles; and a chemiluminescent acridinium

compound bound to avidin or streptavidin to form a solid phase complex; separating the solid phase from the liquid phase; and analyzing the separated solid phase for the presence of chemiluminescent complex. There are several embodiments. In one embodiment, the method comprises the following steps: mixing the ligand antigen, antibody or hapten bound to biotin or a functional derivative thereof with the samole and the antibody directed against the antibody to be detected bound to paramagnetic particles to form a first solid phase complex; adding a chemiluminescent acridinium compound covalently bound to avidin, streptavidin or a functional derivative thereof to form a second solid phase complex; magnetically separating the solid phase from the liquid phase; initiating the chemiluminescent reaction, and analyzing the separated solid phase for the presence of the chemiluminescent complex. Johansen et al. also teaches the method for the quantification of specific antibodies, such as immunoglobulins, wherein a truly parallel reference immunoassay using an identical protocol as a reference. The method comprises measuring the concentration and/or the relative contents of a specific antibody in a liquid sample, wherein the measured light emission of a separated solid phase comprising a captured specific antibody coupled to a chemiluminescent label is compared with the measured light emission obtained in a parallel reference immunoassay wherein the total contents of the class of antibodies in the sample to which said specific antibody belongs is measured. The method comprising the steps of mixing a ligand antigen, hapten towards which the specific antibody to be measured is directly bound to biotin or a functional derivative thereof; an antibody directed against the constant portion of the antibody to be measured bound to

paramagnetic particles and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof with the sample to form a first solid phase from the liquid phase; magnetically separating the first solid phase from the liquid phase; initiating a chemiluminescent reaction and measuring the light emission of the separated first solid phase; mixing a ligand antibody directed against the class of antibodies to be measured bound to biotin or a functional derivative thereof ; an antibody directed against the constant portion of the class of antibodies to be measured bound to paramagnetic particles ; and a chemiluminescent acridinium compound bound to avidin, streptavidin or a functional derivative thereof wherein the term total shall mean the entire amount of the designated class of immunoglobulins (e.g. IgA, IgE, etc.) With the sample to form a second solid phase complex, magnetically separate the second solid phase form the liquid phase; initiating the light emission of the separated first solid phase with that of the separated second solid phase. The specific antibody to be measured in the sample is preferably a specific immunoglobulin selected from the group consisting of IgA, IgD, IgE, IgG, IgM and subclasses thereof. (See col. 3, line 30-col. 5, line 45).

However, Johansen et al. fails to teach using an IgE receptor to bind IgE antibody/ligand complexes and a method of quantification of IgE wherein the IgE to be detected is quantified using both CD23 alone to obtain a first measurement and using FcORII alone to obtain a second measurement.

Johnson et al. teach multiple important roles of CD23 in the regulation of immune responses, particularly the regulation of IgE responses. Among these roles, CD23 acts

as a cellular receptor for IgE and is found in various cell types including B cells. (See col. 1, line 31-col. 2, line 64).

Frank et al. teach detecting IgE antibodies using a human Fc epsilon receptor FcOR. (See col. 1, line 45-col. 2, line 10).

It would have been obvious to one of ordinary skill in the art to use the IgE receptors of Johnson et al. and Frank et al. to measure IgE according to the method of Johansen et al. since both of these receptors, CD23 and FcOR, are specific to IgE antibody and because FcOR and CD23 can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. (See Frank et al. Col. 1, lines 19-34). Regarding claim 16, wherein the number of ligand molecules is between 100% and 200 % of the number of IgE molecules to be detected, it would have been obvious to one of ordinary skills in the art to use enough ligand molecules to optimize binding of all the IgE molecules to be detected. In order to detect 100% of the IgE present in the sample, at least 100% of ligand molecules must be present to bind all the IgE present in the sample.

Claims 6, 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johansen et al. (US 6,087,188) in view of Frank et al. (US 6,060,326) further in view of Arnold, Jr. et al. (US 6,004,745).

Johansen et al. and Frank et al. have been discussed above.

However, Johansen and Frank fail to teach adding label after a first separation step and a second separation to separate the non-complexed labels.

Arnold, Jr. discusses in the background section that a typical sandwich assay involve incubating an immobilized antibody (IgE receptor) with a test medium (sample). Antigens, if in the medium, will bind to the antibody. After incubation, unbound antigen is removed in a separation step. After a second, or simultaneous incubation with a solution of labeled antibody, the bound antigen becomes sandwiched between the immobilized antibody and the labeled antibody. After a second separation step, the amount of labeled antibody can be determined as a measure of the antigen in the medium. (see col. 1, lines 55-66).

It would have been obvious to one of ordinary skill in the art to add the label molecule after a first separation step and then separating the non-complexed labels as discussed in Arnold, Jr. using the reagents in the method of Johansen modified by Frank because such second separation steps, although time consuming, increases the sensitivity of the assay results. Furthermore, since the non-complexed immobilized antibody and the non-complexed labels are separated one at a time, cross-reactivity between the label and the immobilized antibody/reagent is eliminated.

Response to Arguments

The arguments filed on June 16, 2004 have been fully considered but not found persuasive.

Applicants argue that the present invention simulates any interference from other immunoglobulins as well as other potentially interfering component, present in the sample which is in contrast to the teachings of the references cited that teach avoidance of cross-reactivity from other immunoglobulins. Applicants also submit that none of the

cited references recognizes the difference between total IgE and physiologically active IgE and a method of detecting IgE that "allows the binding reactions between the various reactants to be carried out in more in vivo like conditions so as to give an IgE measurement that reflects the ability of IgE to exert its effector functions through binding to its receptor rather than measuring the presence of IgE in a sample".

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the present invention "simulates any interference from other immunoglobulins, as well as any other potentially interfering component, present in the sample" or "a method of detecting IgE that "allows the binding reactions between the various reactants to be carried out in more in vivo like conditions so as to give an IgE measurement that reflects the ability of IgE to exert its effector functions through binding to its receptor rather than measuring the presence of IgE in a sample".) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The limitations as described above are not recited in the claims. Thus, whether or not the present invention simulates any interference from the other immunoglobulins or is "a method of detecting IgE that "allows the binding reactions between the various reactants to be carried out in more in vivo like conditions so as to give an IgE measurement that reflects the ability of IgE to exert its effector functions through binding to its receptor rather than measuring the presence of IgE in a

sample", those limitations are irrelevant to the recited claims and the rejection by the prior arts.

Regarding the 103 rejection by Johansen, Applicants argue that the Office has provided no explanation for why the skilled artisan would be motivated to pick and choose particular features from the two methods-at the expense of leaving the other features out—and then combining such selected features in order to arrive at the present invention. Applicants submit that the Office has failed to consider the teachings of Johansen and Frank 2 as a whole. Applicant further exemplifies that the method of detecting IgE disclosed in Frank 2 and Johansen involve different steps and different reagents. For example, Johansen always mixes the test sample with both IgE binding ligand and an anti-IgE binding antibody while in contrast, Frank 2 involves direct binding of an IgE receptor and IgE in the absence of an IgE binding ligand. Applicants also submit that Frank 2 uses a solid support instead of particles in suspension as in Johansen and argue that such different binding environment would affect the outcome of the performance of the IgE receptor disclosed in Frank 2 when used under experimental conditions of Johansen.

Frank 2 in col. 5, lines 47-56 teaches that :

> In addition, a Fc.sub..epsilon. R formulation of the present invention can include not only a Fc.sub..epsilon. R but ***also one or more additional antigens or antibodies useful in detecting IgE***. As used herein, an antigen refers to any molecule capable of being selectively bound by an antibody. As used herein, specific binding of a first molecule to a second molecule refers to the ability of the first molecule to preferentially bind to (e.g., have higher affinity higher avidity for) the second molecule when compared to the ability of a first molecule to bind to a third molecule. The first molecule need not necessarily be the natural ligand of the second molecule. ***Examples of antibodies used in the present invention include, but are not limited to,***

> ***antibodies that bind selectively to the constant region of an IgE heavy chain (i.e., anti-IgE isotype antibodies) or antibodies that bind selectively to an IgE having a specific antigen specificity (i.e., anti-IgE idiotypic antibodies).*** Examples of antigens used in the present invention include any antigen known to induce the production of IgE. Preferred antigens include allergens and parasite antigens.

Such teaching indicates that Frank 2 uses the same reagents as in the method of Johansen. However, Johansen teaches using the same reagents in a more explicit method steps. Furthermore, if Frank 2 teaches the same method and reagents as in Johansen, then Frank 2 would be applied to a 102 rejection instead of 103 rejection.

The motivation to combine the references has been clearly established in the previous office action. Johansen teaches a method for the quantification of specific antibodies such as immunoglobulins (IgE, IgA, ..). The sample containing the specific antibody is mixed with a ligand antigen (free dissolved ligand of the present invention); an antibody directed against a constant portion of the antibody to be measured bound to a paramagnetic particles and a chemiluminescent acridinium compound as a label; magnetically separating the bound from the unbound; and detect. Johnson uses a CD23, which is specific for IgE antibody. Frank teaches detecting IgE antibodies using a human Fc epsilon receptor (Fc0R). Thus, it would have been obvious to one of ordinary skill in the art to use CD23 or Fc0R as an IgE receptor to measure IgE antibody because these receptors can bind to IgE with less isotype cross-reactivity and more sensitivity than anti-IgE binding antibodies. Regarding claim 16, it is obvious for an ordinary skill in the art to optimize the result by binding all the IgE mocecules to be detected. Regarding Applicants' analysis of the two references about "solid supports vs. suspension of particles", it is well known that solid supports can include particles.

Furthermore, whether a solid support or a particles is used, the antibody/ligand must bind to the solid support or a particle and a step of capturing must be performed. Thus, there is no difference between the reagents of the two methods.

Since the deficiencies, as submitted by the Applicants, in Frank and Johansen have been explained and cure. It is unnecessary to discuss the reference by Johnson.

Regarding the 103 rejection by Johansen in view of Frank 2 and Arnold, Applicants argue that Arnold does not cure the deficiency of motivation as discussed above. Moreover, the combination of Johansen, Frank 2 and Arnold fails to meet all of the limitations of the rejected claims as required. For example, with respect to claim 20, the combination of references still fails to provide a step of adding "a solution of a chemiluminescent compound covalently bound to avidin, streptavidin, or a functional derivative thereof to form a mixture II" (step d).

Since the so-called "deficiencies" of Frank 2 and Johansen have been discussed above. It is unnecessary for Arnold to cure those deficiencies. Since Arnold teaches that solution of labeled antibody is to be applied after the first separation step (see previous office action page 7 following a separation step, Arnold teaches "after a second, or simultaneous incubation with a solution of labeled antibody, the bound antigen becomes sandwiched ..."). Such label solution, taught by Johansen, comprises a chemiluminescent acridinium compound covalently bound to avidin, streptavidin or a functional derivative thereof to form a second solid phase complex.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pensee T. Do
Patent Examiner
December 5, 2003

Christopher L. Chin

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8/31/04